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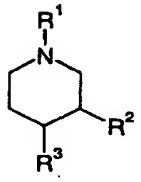

(I)

(57) Abstract

The present invention relates to compounds of general formula (I), wherein R^1 is tetrahydronaphtyl; or $-(CH_2)_n-C_6H_5-R^4$ wherein n is 0–4 and R^4 is H, lower alkyl, or lower alkoxy; or C_5–C_{12} cycloalkyl, optionally substituted by lower alkyl; R^2 is H, OH, lower alkoxy, lower alkenyloxy or lower alkyl; R^3 is C_5–C_7 cycloalkyl or phenyl, optionally substituted by OH, halogen, lower alkoxy, lower alkenyloxy, lower alkyl or $-O-(CH_2)_n-C_6H_5$ wherein n is 0–3; and their pharmaceutically acceptable acid addition salts. The compounds of general formula (I) are suitable for the treatment of memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias such as vascular dementia and AIDS dementia complex, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain conditions, withdrawal symptoms of addictive drugs and reduction of their abuse/craving, control of water balance, Na^+ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

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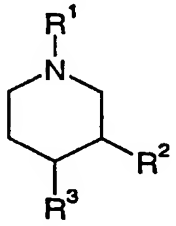
Piperidine Derivatives

The present invention relates to novel compounds of the general formula



I

wherein

R^1 is tetrahydronaphtyl;

or $-(CH_2)_n-C_6H_5-R^4$ wherein n is 0-4 and R^4 is H, lower alkyl, or lower alkoxy;

or C_5-C_{12} cycloalkyl, optionally substituted by lower alkyl;

R^2 is H, OH, lower alkoxy, lower alkenyloxy or lower alkyl;

R^3 is C_5-C_7 cycloalkyl or phenyl, optionally substituted by OH, halogen, lower alkoxy, lower alkenyloxy, lower alkyl or $-O-(CH_2)_n-C_6H_5$ wherein n is 0-3;

and to pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I and their salts are distinguished by valuable therapeutic properties. It has surprisingly been found that the compounds of the present invention are agonist/antagonists of the OFQ receptor. Consequently they will be useful in the treatment of memory and attention

deficits, psychiatric, neurological and physiological disorders, especially, but not limited to, amelioration of symptoms of anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias such as vascular dementia and AIDS dementia complex, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain conditions, withdrawal symptoms of addictive drugs and reduction of their abuse/craving, control of water balance, Na^+ excretion and arterial blood pressure disorders and metabolic disorders such as obesity.

Orphanin FQ (OFQ), a seventeen amino-acid-long peptide (F-G-G-F-T-G-A-R-K-S-A-R-K-L-A-N-Q), has been isolated from rat brain and is a natural ligand for a G-protein coupled receptor (OFQ-R), found at high levels in brain tissue.

OFQ exhibits agonistic activity at the OFQ-R both in vitro and in vivo.

Julius (Nature 377,476, [1995]) discusses the discovery of OFQ noting that this peptide shares greatest sequence similarity with dynorphin A, an established endogenous ligand for opioid receptors. OFQ inhibits adenylate cyclase in CHO(LC 132$^+$) cells in culture and induces hyperalgesia when administered intra-cerebroventricularly to mice. The pattern of results indicate that this heptadecapeptide is an endogenous agonist of the LC 132 receptor and it appears to have pro-nociceptive properties. It has been described that when injected intra-cerebroventricularly in mice, OFQ slows down locomotive activity and induces hyperalgesia and it has been concluded that OFQ may act as a brain neurotransmitter to modulate nociceptive and locomotive behavior.

Exemplary preferred are compounds of the formula I wherein R^1 is C_5-C_{12} cycloalkyl, optionally substituted by lower alkyl, for example the following compounds:

(3RS,4RS)-1-cyclononyl-4-(2-hydroxy-phenyl)piperidin-3-ol hydrochloride (1:1);

1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1);

(3RS,4RS)-1-cyclodecyl-4-(2-isopropyl-phenyl)piperidin-3-ol hydrochloride (1:1);

(3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis-and-(trans-4-isopropylcyclohexyl)-piperidin-3-ol hydrochloride (1:1);

2-(1-cyclodecyl-piperidin-4-yl)-phenol hydrochloride (1:1);

(3RS,4RS)-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1);

1-cyclodecyl-4-cyclohexyl-piperidine hydrochloride (1:1);

(3RS,4RS)-1-cyclononyl-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1);

(3RS,4RS)-4-(2-allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol hydrochloride (1:1);

1-cyclodecyl-4-phenyl-piperidine hydrochloride (1:1);

(3RS,4RS)-1-cyclononyl-4-(2-isopropyl-phenyl)-piperidin-3-ol hydrochloride (1:1); and

(3RS,4RS)-1-cyclodecyl-4-(2-hydroxy-phenyl)piperidin-3-ol hydrochloride (1:1).

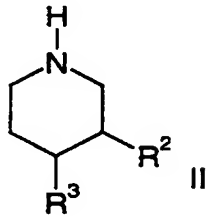
Objects of the present invention are the novel compounds of formula I *per se* and pharmaceutically acceptable addition salts thereof, racemic mixtures and their corresponding enantiomers, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl.

The compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example by processes

described below, which comprise reductively aminating a compound of formula II



II

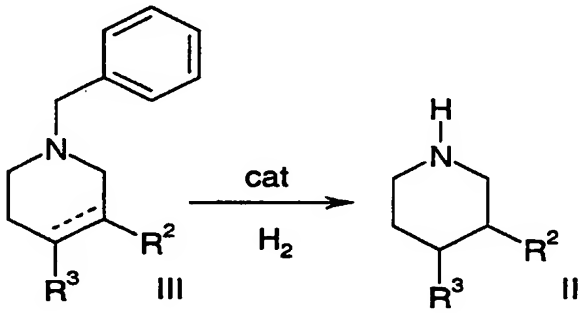
with a compound of formula

IV

wherein R^1, R^2 and R^3 are as described above.

The amination takes place in two steps wherein an imine is formed as intermediate product which further undergoes reduction in the presence of a reductive agent such as sodium cyanoborohydride, molecular hydrogen or nickel.

The amination agent II can be prepared by known methods, for example from compounds of formula III by means of a hydrogenation reaction:



III II

wherein R^2 and R^3 are as described above and, in the case R^3 is cycloalkyl or phenyl substituted by a $-O-CH_2-C_6H_5$, the cleavage of the $-CH_2-C_6H_5$ group takes place during reaction.

The reaction takes place in the presence of hydrogen and a suitable hydrogenation catalyst such as palladium on activated charcoal.

Compounds of formula I, wherein R^2 is hydroxy and/or R^3 is cycloalkyl or phenyl substituted by hydroxy or halogen may be converted into compounds of

formula I, wherein R^2 is lower alkoxy, lower alkenyloxy or lower alkyl and/or R^3 is cycloalkyl or phenyl substituted by lower alkoxy, lower alkenyloxy, lower alkyl or $-O-(CH_2)_n-C_6H_5$, by reacting them for example with alkyl halides, alkenyl halides, phenalkyl halides or lower alcohols in an inert solvent such as anhydrous tetrahydrofuran.

Compounds of formula III can be obtained according to literature procedures (*e.g.* Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317-1319).

If desired, compounds of formula I can be converted into pharmaceutically acceptable acid addition salts. The salt formation is effected at room temperature with methods which are known *per se* and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methanesulphonates, p-toluenesulphonates and the like are examples of such salts.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacodynamic properties. It has been found that the compounds of the present invention are agonist/antagonists of the OFQ receptor and have effects in animal models of memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety, stress disorders, depression, memory loss due to Alzheimer's disease or other dementias such as vascular dementia and AIDS dementia complex, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain conditions, withdrawal symptoms of addictive drugs and reduction of their abuse/craving, control of water balance, Na^+ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

The compounds were investigated in accordance with the tests given hereinafter:

Methods of OFQ-R Binding Assay

Cell Culture

HEK-293 cells adapted to suspension growth (293s) were cultured in HL medium plus 2% FBS. The cells were transfected with the rat OFQ receptor cDNA (LC132), FEBS Lett. 347, 284-288, 1994, cloned in the expression vector

pCEP4 (Invitrogen, SanDiego, CA, USA) using lipofectin (Life Technologies, Bethesda, MD, USA). Transfected cells were selected in the presence of hygromycin (1000 U/ml) (Calbiochem, SanDiego, CA, USA). A pool of resistant cells was tested for OFQ-R expression by binding of [^{3}H]-OFQ (Amersham PLC, Buckinghamshire, England). These cells (293s-OFQ-R) were expanded for large scale culture and membrane preparation.

Membrane preparation

293s-OFQ-R cells were harvested by centrifugation, washed 3 times with phosphate buffered saline (PBS) before resuspension in buffer A (50 mM Tris-HCl, pH 7.8, 5 mM $MgCl_2$, 1 mM EGTA) and disruption with a tissue homogenizer (30 seconds, setting 4, Pt 20, Kinematica, Kriens-Lucern, Switzerland). A total membrane fraction was obtained by centrifugation at 49,000 x g at 4°C. This procedure was repeated twice and the pellet was resuspended in buffer A. Aliquots were stored at -70°C and protein concentrations were determined using the BCA™ Protein Assay Reagent (Pierce, Rockford, IL) following the manufacturer's recommendations.

Binding Assays

[^{3}H]-OFQ competition studies were carried out with 77 µg membrane protein in a final assay volume of 0.5 ml buffer A plus 0.1% BSA and 0.01% bacitracin (Boehringer-Mannheim, Mannheim, Germany) for one hour at room temperature. 50 nM unlabeled OFQ was used to define the non-specific binding. The assays were terminated by filtration through Whatman GF/C filters (Unifilter-96, Canberra Packard S.A., Zurich, Switzerland) pretreated with 0.3% polyethylenimine (Sigma, St. Louis, MO, USA) and 0.1% BSA (Sigma) for 1 hour. The filters were washed 6 times with 1 ml of ice bold 50 mM Tris-HCl pH 7.5. The retained radioactivity was counted on a Packard Top-Count microplate scintillation counter after addition of 40 µl of Microscint 40 (Canberra Packard). The effects of compounds were determined using at least 6 concentrations in triplicate, and determined twice. IC_{50} values were determined by curve fitting and these values were converted to K_i values by the method of Cheng and Prusoff, Biochem. Pharmacol., 22, 3099, 1973.

The affinity to the OFQ-receptor, given as pKi, is in the range of 6,0 to 8,0, for example the pKi for the compounds mentioned below is as follows:

Example	OFQ pKi
4	7.5
36	7.0
19	6.5

4 (3RS,4RS)-1-Cyclononyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

36 (3RS,4RS)-1-Cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

19 Mixture of (3RS,4RS)-4-(2-Methoxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, *e.g.* in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, *e.g.* in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, *e.g.* in the form of suppositories, or parenterally, *e.g.* in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients *e.g.* for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are *e.g.* vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are *e.g.* water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are *e.g.* water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are *e.g.* natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when it appears to be indicated.

The following examples illustrate the present invention, but are not intended to be limiting in any manner.

Example 1

2-(1-Cyclodecyl-piperidin-4-yl)-phenol hydrochloride (1:1)

a) 1-Benzyl-4-(2-benzyloxy-phenyl)-1,2,3,6-tetrahydro-pyridine

The title compound was prepared in comparable yield according to a literature procedure (Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317 - 1319) in two steps starting from 2-benzyloxybromobenzene instead of 2-bromoanisole. The product was obtained as a light brown oil.

MS m/e (%): 356 ($M+H^+$, 100).

b) 2-Piperidin-4-yl-phenol

To a solution of 37.6 g (0.105 mol) of 1-benzyl-4-(2-benzyloxy-phenyl)-1,2,3,6-tetrahydro-pyridine in 380 ml of methanol were added 7.0 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated

(room temperature, 5 bar) until the theoretical amount of hydrogen was taken up (about 20 h). The catalyst was filtered off and was washed three times with 50 ml portions of methanol. The filtrate was evaporated *in vacuo* and purified by flash-chromatography to give 14.8 g (80%) of the title compound as a light brown foam.

MS m/e (%): 177 (M^+, 100).

c) 2-(1-Cyclodecyl-piperidin-4-yl)-phenol

To a suspension of 1.0 g (5.64 mmol) 2-piperidin-4-yl-phenol in 870 mg (5.64 mmol) cyclodecanone were added 8.0 g (28 mmol) tetraisopropyl orthotitanate. After stirring for 4 days at room temperature, a viscous oil was obtained. A solution of 250 mg (3.95 mmol) sodium cyanoborohydride in 4 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 2 h at room temperature and 10 ml 2.5 M ammonia in ethanol were added. The precipitate was filtered off and the filtrate evaporated. The residue was purified by flash-chromatography to give 1.37 g (77%) of the title compound as a light yellow foam.

MS m/e (%): 316 ($M+H^+$, 100).

d) 2-(1-Cyclodecyl-piperidin-4-yl)-phenol hydrochloride (1:1)

To a solution of 100 mg (0.32 mmol) 2-(1-cyclodecyl-piperidin-4-yl)-phenol in 20 ml ether were added 1 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 10 ml ether. Filtration of the precipitate and washing with ether gave 101 mg (91%) of the title compound as a white powder.

MS m/e (%): 316 ($M+H^+$, 100).

Example 2

1-Cyclodecyl-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 100 mg (0.32 mmol) 2-(1-cyclodecyl-piperidin-4-yl)-phenol (example 1c) in 1 ml anhydrous tetrahydrofuran at 0°C were added 76 mg (0.38 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 55 mg (0.38 mmol) methyl iodide were added. After

stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

The solvent was removed and the residue was purified by flash-chromatography to give 74 mg of an oil. The amine was dissolved in 5 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 42 mg (36%) of the title compound as a white powder.

MS m/e (%): 330 ($M+H^+$, 100).

Example 3

4-(2-Allyloxy-phenyl)-1-cyclodecyl-piperidine hydrochloride (1:1)

To a solution of 200 mg (0.64 mmol)) 2-(1-cyclodecyl-piperidin-4-yl)-phenol (example 1c) in 2 ml anhydrous tetrahydrofuran at 0°C were added 152 mg (0.76 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 92 mg (0.76 mmol) allyl bromide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

The solvent was removed and the residue was purified by flash-chromatography to give 164 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 138 mg (55%) of the title compound as a white powder.

MS m/e (%): 356 ($M+H^+$, 100).

Example 4

(3RS,4RS)-1-Cyclononyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-1-Benzyl-4-(2-benzyloxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

The title compound was prepared in comparable yield according to a literature procedure (Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317 - 1319) in three steps starting from 2-benzyloxybromobenzene instead of 2-bromoanisole. The product was obtained as white crystals.

MS m/e (%): 374 ($M+H^+$, 100).

b) (3RS,4RS)-4-(2-Hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 46.5 g (0.11 mol) of (3RS,4RS)-1-benzyl-4-(2-benzyloxy-phenyl)-piperidin-3-ol hydrochloride (1:1) in 1100 ml of methanol were added 8.5 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature, 5 bar) until the theoretical amount of hydrogen was taken up (about 20 h). The catalyst was filtered off and was washed three times with 100 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 21.0 g (99%) of the title compound as a white powder.

MS m/e (%): 193 (M^+, 78), 164 (58), 44 (100).

c) (3RS,4RS)-4-(2-Hydroxy-phenyl)-piperidin-3-ol

To a solution of 3.17 g (1.38 mmol) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1) in 30 ml methanol were added 1.5 g sodium carbonate. After stirring for 1h at room temperature, the sodium salts were filtered off and washed with 10 ml of ethanol. The filtrate was concentrated, diluted with ethanol and filtered again. The filtrate was evaporated to give 2.7 g (quantitative) of the title compound as a white solid.

MS m/e (%): 194 ($M+H^+$, 100).

d) (3RS,4RS)-1-cyclononyl-4-(2-hydroxy-phenyl)-piperidin-3-ol

To a suspension of 520 mg (2.69 mmol) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol in 380 mg (1.55 mmol) cyclononanone were added 3.80 g (13 mmol) tetraisopropyl orthotitanate. After stirring for 2 days at room temperature, a viscous oil was obtained. A solution of 120 mg (1.9 mmol) sodium cyanoborohydride in 1 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 6 h at room temperature and 2 ml 2.5 M ammonia in ethanol were added. The precipitate was filtered off and the filtrate evaporated. The residue was purified by flash-chromatography to give 435 mg (51%) of the title compound as a light yellow foam.

MS m/e (%): 318 ($M+H^+$, 100).

e) (3RS,4RS)-1-Cyclononyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 100 mg (0.32 mmol) (3RS,4RS)-1-cyclononyl-4-(2-hydroxy-phenyl)-piperidin-3-ol in 10 ml ether were added 1 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 10 ml ether. Filtration of the precipitate and washing with ether gave 98 mg (88%) of the title compound as a white powder.

MS m/e (%): 318 ($M+H^+$, 100).

Example 5

(3RS,4RS)-1-Cyclononyl-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 110 mg (0.35 mmol) (3RS,4RS)-1-cyclononyl-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 4d) in 1 ml anhydrous tetrahydrofuran at 0°C were added 85 mg (0.42 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 59 mg (0.42 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

The solvent was removed and the residue was purified by flash-chromatography to give 74 mg of an oil. The amine was dissolved in 5 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 70 mg (54%) of the title compound as a white powder.

MS m/e (%): 332 ($M+H^+$, 100).

Example 6

(3RS,4RS)-1-Cyclodecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a suspension of 2.50 g (12.9 mmol) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 4c) in 2.00 g (12.9 mmol) cyclodecanone were added 4.58 g (16.1 mmol) tetraisopropyl orthotitanate. After stirring overnight at room temperature, a viscous oil was obtained. A solution of 570 mg (9 mmol)

sodium cyanoborohydride in 10 ml ethanol was added dropwise within 1 min. Stirring was continued at room temperature overnight and 50 ml of 1 N hydrochloric acid solution were added. After 30 min, the precipitate was filtered off and washed with 1 N hydrochloric acid solution to give 2.81 g (59%) of the title compound as a light brown foam.

MS m/e (%): 332 ($M+H^+$, 100).

Example 7

(3RS,4RS)-1-Cyclodecyl-4-(2-ethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-1-Cyclodecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol

To a solution of 570 mg (1.55 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1) (example 6) in 20 ml ethanol were added 1.5 g sodium carbonate. After stirring for 1h at room temperature, the sodium salts were filtered off and washed with 10 ml of ethanol. The filtrate was evaporated to give 510 mg (quantitative) of the title compound as a white solid.

MS m/e (%): 332 ($M+H^+$, 100).

b) (3RS,4RS)-1-Cyclodecyl-4-(2-ethoxy-phenyl)-piperidin-3-ol

To a solution of 204 mg (0.62 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol in 1 ml anhydrous tetrahydrofuran at 0°C were added 147 mg (0.74 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 74 mg (0.68 mmol) ethyl bromide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

The solvent was removed and the residue was purified by flash-chromatography to give 51 mg (23%) of the title compound as a colourless oil.

MS m/e (%): 360 ($M+H^+$, 100).

c) (3RS,4RS)-1-Cyclodecyl-4-(2-ethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 7 mg (0.02 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-ethoxy-phenyl)-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.5 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 2 ml ether. Filtration of the precipitate and washing with ether gave 7 mg (quantitative) of the title compound as white crystals.

MS m/e (%): 360 ($M+H^+$, 100).

Example 8

(3RS,4RS)-1-Cyclodecyl-3-ethoxy-4-(2-ethoxy-phenyl)-piperidine hydrochloride (1:1)

a) (3RS,4RS)-1-Cyclodecyl-3-ethoxy-4-(2-ethoxy-phenyl)-piperidine

The title compound was obtained as side product during the isolation and purification of (3RS,4RS)-1-Cyclodecyl-4-(2-ethoxy-phenyl)-piperidin-3-ol (example 7b). Flash-chromatography gave 93 mg (38 mg) of the title compound, as a light brown oil.

MS m/e (%): 388 ($M+H^+$, 100).

b) (3RS,4RS)-1-Cyclodecyl-3-ethoxy-4-(2-ethoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 10 mg (0.025 mmol) (3RS,4RS)-1-cyclodecyl-3-ethoxy-4-(2-ethoxy-phenyl)-piperidine in 1 ml ether were added 0.2 ml 2.5 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 2 ml ether. Filtration of the precipitate and washing with ether gave 10 mg (quantitative) of the title compound as white crystals.

MS m/e (%): 388 ($M+H^+$, 100).

Example 9

(3RS,4RS)-4-(2-Allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-4-(2-Allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol

To a solution of 645 mg (1.96 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 7a) in 6 ml anhydrous acetone were added 298 mg (2.15 mmol) potassium carbonate and 260 mg (2.15 mmol) allyl bromide. After stirring at 60°C overnight, the product was extracted with three 10 ml portions of ethyl acetate, washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 557 mg (76%) of the title compound as a white powder.

MS m/e (%): 372 ($M+H^+$, 100).

b) (3RS,4RS)-4-(2-Allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol hydrochloride (1:1)

To a solution of 133 mg (0.36 mmol) (3RS,4RS)-4-(2-allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol in 2.5 ml tetrahydrofuran were added 2 ml 2.5 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 10 ml ether. Filtration of the precipitate and washing with ether gave 100 mg (68%) of the title compound as white crystals.

MS m/e (%): 372 ($M+H^+$, 100).

Example 10

(3RS,4RS)-4-(2-Allyloxy-phenyl)-1-cyclodecyl-3-methoxy-piperidine hydrochloride (1:1)

To a solution of 133 mg (0.36 mmol) (3RS,4RS)-4-(2-allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol (example 9a) in 1.5 ml anhydrous tetrahydrofuran at 0°C were added 85 mg (0.43 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 61 mg (0.43 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 77 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 67 mg (44%) of the title compound as a white powder.

MS m/e (%): 386 ($M+H^+$, 100).

Example 11

(3RS,4RS)-1-Cyclodecyl-3-methoxy-4-(2-propoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 30 mg (0.07 mmol) of (3RS,4RS)-4-(2-allyloxy-phenyl)-1-cyclodecyl-3-methoxy-piperidine hydrochloride (1:1) (example 10) in 1.5 ml of methanol were added 10 mg of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature, 1 bar) overnight. The catalyst was filtered off and was washed three times with 1 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 23 mg (77%) of the title compound as a white powder.

MS m/e (%): 388 ($M+H^+$, 100).

Example 12

(3RS,4RS)-4-(2-Benzyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol hydrochloride (1:1)

To a solution of 721 mg (1.96 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1) (example 6) in 3 ml anhydrous dimethylformamide were added 810 mg (5.88 mmol) potassium carbonate and 370 mg (2.16 mmol) benzyl bromide. After stirring at 60°C overnight, the product was extracted with three 10 ml portions of ethyl acetate, washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 90 mg of a light yellow solid. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 63 mg (7%) of the title compound as a white powder.

MS m/e (%): 422 ($M+H^+$, 100).

Example 13

(3RS,4RS)-1-Cycloundecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-1-Cycloundecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol

To a suspension of 300 mg (1.55 mmol) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 4c) in 260 mg (1.55 mmol) cycloundecanone were added 2.20 g (7.8 mmol) tetraisopropyl orthotitanate. After stirring for 6 days at room temperature, a viscous oil was obtained. A solution of 70 mg (1.1 mmol) sodium cyanoborohydride in 1 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 6 h at room temperature and 2 ml 2.5 M ammonia in ethanol were added. The precipitate was filtered off and the filtrate evaporated. The residue was purified by flash-chromatography to give 138 mg (26%) of the title compound as a light yellow foam.

MS m/e (%): 346 ($M+H^+$, 100).

b) (3RS,4RS)-1-Cycloundecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 7 mg (0.02 mmol) (3RS,4RS)-1-cycloundecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 1 ml ether. Filtration of the precipitate and washing with ether gave 7 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 346 ($M+H^+$, 100).

Example 14

(3RS,4RS)-1-Cycloundecyl-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 110 mg (0.31 mmol) (3RS,4RS)-1-cycloundecyl-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 13a) in 1 ml anhydrous tetrahydrofuran at 0°C were added 65 mg (0.34 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 48 mg (0.34 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 70 mg of an oil. The amine was dissolved in 5 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added

dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 65 mg (55%) of the title compound as a white powder.

MS m/e (%): 360 ($M+H^+$, 100).

Example 15

Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-2-yl]-piperidin-3-ol hydrochloride (1:1)

a) Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-2-yl]-piperidin-3-ol

To a mixture of 300 mg (1.55 mmol) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 4c) and 230 mg (1.55 mmol) β-tetralone were added 2.20 g (7.8 mmol) tetraisopropyl orthotitanate. After stirring for 5 days at room temperature, a viscous oil was obtained. A solution of 70 mg (1.1 mmol) sodium cyanoborohydride in 1 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 6 h at room temperature and 2 ml 2.5 M ammonia in ethanol were added. The precipitate was filtered off and the filtrate evaporated. The residue was purified by flash-chromatography to give 100 mg (20%) of the title compound as a light brown foam.

MS m/e (%): 324 ($M+H^+$, 100).

b) Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-2-yl]-piperidin-3-ol hydrochloride (1:1)

To a solution of 7 mg (0.02 mmol) of the mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-2-yl]-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 1 ml ether. Filtration of the precipitate and washing with ether gave 7 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 324 ($M+H^+$, 100).

Example 16

Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-methoxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-2-yl]-piperidin-3-ol hydrochloride (1:1)

To a solution of 78 mg (0.24 mmol) of the mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-2-yl]-piperidin-3-ol (example 15a) in 0.8 ml anhydrous tetrahydrofuran at 0°C were added 55 mg (0.27 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 38 mg (0.27 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 38 mg of a foam. The amine was dissolved in 3 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 40 mg (44%) of the title compound as a light brown powder.

MS m/e (%): 338 ($M+H^+$, 100).

Example 17

Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperidin-3-ol hydrochloride (1:1)

a) Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperidin-3-ol

To a mixture of 300 mg (1.55 mmol) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 4c) and 230 mg (1.55 mmol) α-tetralone were added 2.20 g (7.8 mmol) tetraisopropyl orthotitanate. After stirring for 5 days at room temperature, a viscous oil was obtained. A solution of 70 mg (1.1 mmol) sodium cyanoborohydride in 1 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 6 h at room temperature and 2 ml 2.5 M ammonia in ethanol were added. The precipitate was filtered off and the filtrate evaporated. The residue was purified by flash-chromatography to give 29 mg (6%) of the title compound as a light brown foam.

MS m/e (%): 324 ($M+H^+$, 100).

b) Mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperidin-3-ol hydrochloride (1:1)

To a solution of 4 mg (0.01 mmol) of the mixture of (3RS,4RS)- and (3SR,4SR)-4-(2-hydroxy-phenyl)-1-[(RS)-1,2,3,4-tetrahydro-naphthalen-1-yl]-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 1 ml ether. Filtration of the precipitate and washing with ether gave 4 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 324 ($M+H^+$, 100).

Example 18

Mixture of (3RS,4RS)-4-(2-Hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

a) Mixture of (3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol

To a suspension of 2.50 g (12.9 mmol)) (3RS,4RS)-4-(2-hydroxy-phenyl)-piperidin-3-ol (example 4c) in 1.88 g (12.9 mmol) 4-isopropylcyclohexanone were added 9.16 g (32.2 mmol) tetraisopropyl orthotitanate. After stirring overnight at room temperature, a viscous oil was obtained. A solution of 570 mg (9 mmol) sodium cyanoborohydride in 10 ml ethanol was added dropwise within 1 min. Stirring was continued at room temperature overnight and 50 ml of 1 N hydrochloric acid solution were added. After 30 min, the precipitate was filtered off and washed with 1 N hydrochloric acid solution to give 1.51 g of a white solid. The mother liquor was extracted with dichloromethane and the extract was combined with the first precipitate. Purification by flash-chromatography gave 1.90 g (46%) of the title compound as a white solid.

MS m/e (%): 318 ($M+H^+$, 100).

b) Mixture of (3RS,4RS)-4-(2-Hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 10 mg (0.03 mmol) of the mixture of (3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.5 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 1 ml ether. Filtration of the precipitate and washing with ether gave 10 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 318 ($M+H^+$, 100).

Example 19

Mixture of (3RS,4RS)-4-(2-Methoxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 75 mg (0.24 mmol) of the mixture of (3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol (example 18a) in 1 ml anhydrous tetrahydrofuran at 0°C were added 103 mg (0.52 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 70 mg (0.49 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

The solvent was removed and the residue was purified by flash-chromatography to give 7 mg of an oil. The amine was dissolved in 1 ml ether and 0.2 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 7 mg (8%) of the title compound as a white powder.

MS m/e (%): 332 ($M+H^+$, 100).

Example 20

Mixture of (3RS,4RS)-4-(2-allyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

a) Mixture of (3RS,4RS)-4-(2-allyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol

To a solution of 700 mg (2.2 mmol) of the mixture of (3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol (example 18a) in 3 ml anhydrous dimethylformamide were added 610 mg (4.4 mmol) potassium carbonate and 320 mg (2.64 mmol) allyl bromide. After stirring at 60°C overnight, the solvent was removed and the residue was purified by flash-chromatography to give 125 mg (16%) of the title compound as a colourless foam.

MS m/e (%): 358 ($M+H^+$, 100).

b) Mixture of (3RS,4RS)-4-(2-allyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 5 mg (0.014 mmol) of the mixture of (3RS,4RS)-4-(2-allyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 1 ml ether. Filtration of the precipitate and washing with ether gave 5 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 358 ($M+H^+$, 100).

Example 21

Mixture of (3RS,4RS)-4-(2-Allyloxy-phenyl)-1-(cis- and trans-4-isopropyl-cyclohexyl)-3-methoxy-piperidine hydrochloride (1:1)

To a solution of 50 mg (0.14 mmol) of the mixture of (3RS,4RS)-4-(2-allyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol (example 20a) in 0.5 ml anhydrous tetrahydrofuran at 0°C were added 33 mg (0.17 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 24 mg (0.17 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 30 mg of an oil. The amine was dissolved in 2 ml ether and 0.5 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 32 mg (56%) of the title compound as a white powder.

MS m/e (%): 372 ($M+H^+$, 100).

Example 22

Mixture of (3RS,4RS)-4-(2-benzyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

a) Mixture of (3RS,4RS)-4-(2-benzyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol

To a solution of 397 mg (1.25 mmol) of the mixture of (3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol (example 18a) in 3 ml anhydrous dimethylformamide were added 912 mg (6.6 mmol) potassium carbonate and 450 mg (2.64 mmol) benzyl bromide. After stirring at 60°C overnight, the solvent was removed and the residue was purified by flash-chromatography to give 228 mg (45%) of the title compound as a colourless foam.

MS m/e (%): 408 ($M+H^+$, 100).

b) Mixture of (3RS,4RS)-4-(2-benzyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 7 mg (0.017 mmol) of the mixture of (3RS,4RS)-4-(2-benzyloxy-phenyl)-1-(cis- and -(trans-4-isopropyl-cyclohexyl)-piperidin-3-ol in 1 ml ether were added 0.2 ml 2.3 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 1 ml ether. Filtration of the precipitate and washing with ether gave 7 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 408 ($M+H^+$, 100).

Example 23

(3RS,4RS)-1-Benzyl-3-methoxy-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

a) (3RS,4RS)-1-Benzyl-4-(2-methoxy-phenyl)-piperidin-3-ol

The title compound was prepared in comparable yield according to a literature procedure (Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317 - 1319) in three steps starting from 2-bromoanisole. The product was obtained as a white powder.

MS m/e (%): 298 ($M+H^+$, 100).

b) (3RS,4RS)-1-Benzyl-3-methoxy-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 149 mg (0.5 mmol) (3RS,4RS)-1-benzyl-4-(2-methoxy-phenyl)-piperidin-3-ol in 1.5 ml anhydrous tetrahydrofuran at 0°C were added 126 mg (0.6 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h

at this temperature and 85 mg (0.6 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 128 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 130 mg (75%) of the title compound as a white powder.

MS m/e (%): 312 ($M+H^+$, 100).

Example 24

(3RS,4RS)-3-Methoxy-1-(2-methoxy-benzyl)-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

a) (3RS,4RS)-3-Methoxy-4-(2-methoxy-phenyl)-piperidine

To a solution of 4.03 g (11.6 mol) (3RS,4RS)-1-benzyl-3-methoxy-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1) (example 23b) in 100 ml of methanol were added 1.0 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature, 1 bar) for 20 h. The catalyst was filtered off and was washed three times with 10 ml portions of methanol. The filtrate was concentrated to a total volume of ca. 50 ml and 1.3 g sodium carbonate were added. After stirring the suspension for additional 2 h, the solvent was removed under reduced pressure and the residue was re-suspended in 50 ml dichloromethane. Inorganic salts were filtered off and the filtrate was evaporated to give 2.20 g (74%) of the title compound as a light yellow oil.

MS m/e (%): 221 (M^+, 17), 189 (100), 178 (62).

b) (3RS,4RS)-3-Methoxy-1-(2-methoxy-benzyl)-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 111 mg (0.5 mmol) (3RS,4RS)-3-methoxy-4-(2-methoxy-phenyl)-piperidine in 1.5 ml methanol were added 75 mg (0.55 mmol) 2-methoxybenzaldehyde. The reaction mixture was stirred for 5 min at room temperature and 63 mg (1.0 mmol) sodium cyanoborohydride were added.

After reaction overnight, 1 ml 2.3 M hydrochloric acid in methanol was added. The reaction mixture was evaporated, re-dissolved in 5 ml water and was washed with ether. The aqueous solution was adjusted to pH 10 by addition of solid potassium hydroxide and was extracted with dichloromethane, dried (magnesium sulfate), evaporated and purified by flash-chromatography to give 100 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 70 mg (35%) of the title compound as a white powder.

MS m/e (%): 342 ($M+H^+$, 100).

Example 25

(3RS,4RS)-3-Methoxy-4-(2-methoxy-phenyl)-1-(3-phenyl-propyl)-piperidine hydrochloride (1:1)

To a solution of 111 mg (0.5 mmol) (3RS,4RS)-3-methoxy-4-(2-methoxy-phenyl)-piperidine (example 24a) in 1.5 ml methanol were added 74 mg (0.55 mmol) 3-phenylpropionaldehyde. The reaction mixture was stirred for 5 min at room temperature and 63 mg (1.0 mmol) sodium cyanoborohydride were added. After reaction overnight, 1 ml 2.3 M hydrochloric acid in methanol was added. The reaction mixture was evaporated, re-dissolved in 5 ml water and was washed with ether. The aqueous solution was adjusted to pH 10 by addition of solid potassium hydroxide and was extracted with dichloromethane, dried (magnesium sulfate) and evaporated to give 155 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 150 mg (80%) of the title compound as a white powder.

MS m/e (%): 340 ($M+H^+$, 100).

Example 26

(3RS,4RS)-1-(4-tert-Butyl-benzyl)-3-methoxy-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 111 mg (0.5 mmol) (3RS,4RS)-3-methoxy-4-(2-methoxy-phenyl)-piperidine (example 24a) in 1.5 ml methanol were added 89 mg (0.55 mmol) 4-tert-butylbenzaldehyde. The reaction mixture was stirred for 5 min at

room temperature and 63 mg (1.0 mmol) sodium cyanoborohydride were added. After reaction overnight, 1 ml 2.3 M hydrochloric acid in methanol was added. The reaction mixture was evaporated, re-dissolved in 5 ml water and was washed with ether. The aqueous solution was adjusted to pH 10 by addition of solid potassium hydroxide and was extracted with dichloromethane, dried (magnesium sulfate), evaporated and purified by flash-chromatography to give 100 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 110 mg (55%) of the title compound as a white powder.

MS m/e (%): 368 ($M+H^+$, 100).

Example 27

(3RS,4RS)-3-Allyloxy-1-benzyl-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 149 mg (0.5 mmol) (3RS,4RS)-1-benzyl-4-(2-methoxy-phenyl)-piperidin-3-ol (example 23a) in 1.5 ml anhydrous tetrahydrofuran at 0°C were added 126 mg (0.6 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 73 mg (0.6 mmol) allyl bromide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 149 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 150 mg (80%) of the title compound as a white powder.

MS m/e (%): 338 ($M+H^+$, 100).

Example 28

(3RS,4RS)-1-Cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-4-(2-Methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

A solution of 5.95 g (20 mmol) of (3RS,4RS)-1-benzyl-4-(2-methoxy-phenyl)-piperidine-3-ol (example 23a) in 100 ml 1 N hydrochloric acid solution in ethanol was stirred for 30 min. The solvent and excess hydrochloric acid were removed *in vacuo*. The residue was dissolved in 100 ml of methanol and 1.5 g of 10 % of palladium on activated charcoal were added. The reaction mixture was hydrogenated (room temperature, 1 bar) for 20 h. The catalyst was filtered off and was washed three times with 10 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 4.7 g (96%) of the title compound as a white powder.

MS m/e (%): 207 (M^+, 19), 178 (100).

b) (3RS,4RS)-4-(2-Methoxy-phenyl)-piperidin-3-ol

To a suspension of 4.7 g (20 mmol) (3RS,4RS)-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1) in 40 ml methanol were added 2.1 g sodium carbonate. After stirring for 1h at room temperature, the sodium salts were filtered off and washed with 10 ml of methanol. The filtrate was concentrated, diluted with 2-propanol and filtered again. The filtrate was evaporated to give 4.10 g (quantitative) of the title compound as a white solid.

MS m/e (%): 208 ($M+H^+$, 100).

c) (3RS,4RS)-1-Cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol

To a suspension of 4.14 g (20 mmol) (3RS,4RS)-4-(2-methoxy-phenyl)-piperidin-3-ol in 3.09 g (20 mmol) cyclodecanone were added 7.12 g (25 mmol) tetraisopropyl orthotitanate. After stirring overnight at room temperature, a viscous oil was obtained. A solution of 880 mg (14 mmol) sodium cyanoborohydride in 20 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 48 h at room temperature and 10 ml of 25 % hydrochloric acid were added. After 30 min, the precipitate was filtered off and 200 ml 2.5 M ammonia in ethanol were added. The precipitate was filtered off again and the filtrate evaporated. The residue was purified by flash-chromatography to give 5.40 g (78%) of a light yellow oil that crystallized upon standing at room temperature.

MS m/e (%): 346 ($M+H^+$, 100).

d) (3RS,4RS)-1-Cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 270 mg (0.78 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol in 10 ml ether were added 2 ml 2.5 N hydrochloric acid in ether. After stirring for 30 min, excess hydrochloric acid and ether were removed *in vacuo* and the residue was re-suspended in 20 ml ether. Filtration of the precipitate and washing with ether gave 298 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 346 ($M+H^+$, 100).

Example 29

(3RS,4RS)-3-Methoxy-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 173 mg (0.5 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol (example 28c) in 1.5 ml anhydrous tetrahydrofuran at 0°C were added 126 mg (0.6 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 85 mg (0.6 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 120 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 133 mg (67%) of the title compound as a white powder.

MS m/e (%): 360 ($M+H^+$, 100).

Example 30

(3RS,4RS)-3-Allyloxy-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

a) (3RS,4RS)-3-Allyloxy-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine

To a solution of 146 mg (1.0 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol (example 28c) in 3.0 ml anhydrous tetrahydrofuran at 0°C were added 256 mg (1.2 mmol) potassium bis(trimethylsilyl)amide.

Stirring was continued for 1h at this temperature and 145 mg (1.2 mmol) allyl bromide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 4 ml water, the product was extracted with three 20 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 280 mg (73%) the title compound as a colourless oil.

MS m/e (%): 386 ($M+H^+$, 100).

b) (3RS,4RS)-3-Allyloxy-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine hydrochloride (1:1)

To a solution of 100 mg (0.26 mmol) (3RS,4RS)-3-allyloxy-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine in 10 ml ether was added dropwise 1 ml of 2.3 M hydrochloric acid in ether. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 109 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 386 ($M+H^+$, 100).

Example 31

(3RS,4RS)-1-Cyclodecyl-4-(2-methoxy-phenyl)-3-propoxy-piperidine hydrochloride (1:1)

To a solution of 77 mg (0.2 mmol) (3RS,4RS)-3-allyloxy-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine (example 30a) in 10 ml of ethyl acetate were added 40 mg of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature, 1 bar) for 20 h. The catalyst was filtered off and was washed three times with 1 ml portions of ethyl acetate. The filtrate was evaporated *in vacuo* to give 78 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 85 mg (quantitative) of the title compound as a white powder.

MS m/e (%): 388 ($M+H^+$, 100).

Example 32

(3RS,4RS)-1-Cyclodecyl-4-(2-isopropyl-phenyl)-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-1-Benzyl-4-(2-isopropyl-phenyl)-piperidin-3-ol

The title compound was prepared in comparable yield according to a literature procedure (Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317 - 1319) in three steps starting from 2-bromoisopropylbenzene instead of 2-bromoanisole. The product was obtained as a white solid.

MS m/e (%): 310 ($M+H^+$, 100).

b) (3RS,4RS)-4-(2-Isopropyl-phenyl)-piperidin-3-ol hydrochloride (1:1)

A solution of 10.9 g (32 mmol) of (3RS,4RS)-1-benzyl-4-(2-isopropyl-phenyl)-piperidin-3-ol in 100 ml 1 N hydrochloric acid solution in ethanol was stirred for 30 min. The solvent and excess hydrochloric acid were removed *in vacuo*. The residue was dissolved in 300 ml of methanol and 2.4 g of 10 % of palladium on activated charcoal were added. The reaction mixture was hydrogenated (room temperature, 5 bar) for 20 h. The catalyst was filtered off and was washed three times with 50 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 5.9 g (74%) of the title compound as a white powder.

MS m/e (%): 219 (M^+, 17), 202 (21), 190 (39), 172 (42), 44 (100).

c) (3RS,4RS)-4-(2-Isopropyl-phenyl)-piperidin-3-ol

To a suspension of 5.75 g (22.6 mmol) (3RS,4RS)-4-(2-isopropyl-phenyl)-piperidin-3-ol hydrochloride (1:1) in 150 ml ethanol were added 3.6 g sodium carbonate. After stirring for 2h at room temperature, the sodium salts were filtered off and washed with 10 ml of ethanol. The filtrate was concentrated, diluted with 2-propanol and filtered again. The filtrate was evaporated to give 4.93 g (quantitative) of the title compound as a white solid.

MS m/e (%): 220 ($M+H^+$, 100).

d) (3RS,4RS)-1-Cyclodecyl-4-(2-isopropyl-phenyl)-piperidin-3-ol

To a suspension of 500 mg (2.28 mmol) (3RS,4RS)-4-(2-isopropyl-phenyl)-piperidin-3-ol in 350 mg (2.28 mmol) cyclodecanone were added 3.24 g (11.4 mmol) tetraisopropyl orthotitanate. After stirring for 5 days at room temperature, a viscous oil was obtained. A solution of 100 mg (1.59 mmol) sodium cyanoborohydride in 2 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 4 h at room temperature and 25 ml of 2.3 N hydrochloric acid in ethanol were added. After heating for 3 h at 60°C, the solution was adjusted to pH 8 by addition of 25 % sodium hydroxide solution and filtered. The filtrate was extracted with ethyl acetate, the organic phase washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 415 mg (51%) of the title compound as a white solid.

MS m/e (%): 358 ($M+H^+$, 100).

e) (3RS,4RS)-1-Cyclodecyl-4-(2-isopropyl-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 30 mg (0.08 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-isopropyl-phenyl)-piperidin-3-ol in 3 ml ethanol were added dropwise 0.3 ml of 2.3 M hydrochloric acid in ethanol. The solution was stirred for 30 min at room temperature and was evaporated. The residue was suspended in ether and was stirred for 1 h. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 23 mg (70%) of the title compound as a white powder.

MS m/e (%): 358 ($M+H^+$, 100).

Example 33

(3RS,4RS)-1-Cyclodecyl-4-(2-isopropyl-phenyl)-3-methoxy-piperidine hydrochloride (1:1)

To a solution of 200 mg (0.56 mmol) (3RS,4RS)-1-cyclodecyl-4-(2-isopropyl-phenyl)-piperidin-3-ol (example 32d) in 2 ml anhydrous tetrahydrofuran at 0°C were added 134 mg (0.67 mmol) potassium bis(trimethylsilyl)amide. Stirring was continued for 1h at this temperature and 80 mg (0.56 mmol) methyl iodide were added. After stirring for 30 minutes at 0°C, the ice bath was removed and the reaction mixture was allowed to warm up to room temperature overnight.

After addition of 2 ml water, the product was extracted with three 10 ml portions of ether, dried (magnesium sulfate) and evaporated. The residue was

purified by flash-chromatography to give 50 mg of an oil. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 34 mg (15%) of the title compound as a white powder.

MS m/e (%): 372 ($M+H^+$, 100).

Example 34

(3RS,4RS)-1-Cyclononyl-4-(2-isopropyl-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a suspension of 200 mg (0.91 mmol) (3RS,4RS)-4-(2-isopropyl-phenyl)-piperidin-3-ol (example 32c) in 160 mg (1.14 mmol) cyclononanone were added 1.29 g (4.56 mmol) tetraisopropyl orthotitanate. After stirring for 6 days at room temperature, a viscous oil was obtained. A solution of 24 mg (0.64 mmol) sodium borohydride in 2 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 1 h at room temperature and 10 ml of 2.3 N hydrochloric acid in ethanol were added. After heating for 4 h at 60°C, the solution was adjusted to pH 8 by addition of 25 % sodium hydroxide solution and filtered. The filtrate was extracted with ethyl acetate, the organic phase washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 160 mg of a light yellow oil. The amine was dissolved in 10 ml ethanol and 1 ml of 2.3 M hydrochloric acid in ethanol was added dropwise. The solution was stirred for 30 min at room temperature and was evaporated. The residue was suspended in ether and was stirred for 1 h. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 175 mg (51%) of the title compound as a white powder.

MS m/e (%): 344 ($M+H^+$, 100).

Example 35

1-Cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidine hydrochloride (1:1)

a) 1-Benzyl-4-(2,6-dimethoxy-phenyl)-1,2,3,6-tetrahydro-pyridine

The title compound was prepared in comparable yield according to a literature procedure (Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317 - 1319) in two steps starting from 1,3-dimethoxyphen-2-ylmagnesium

bromide instead of 2-methoxyphenylmagnesium bromide. The product was obtained as white needles.

MS m/e (%): 310 ($M+H^+$, 100).

b) 4-(2,6-Dimethoxy-phenyl)-piperidine

A solution of 3.4 g (11 mmol) of 1-benzyl-4-(2,6-dimethoxy-phenyl)-1,2,3,6-tetrahydro-pyridine in 100 ml 1 N hydrochloric acid solution in ethanol was stirred for 30 min. The solvent and excess hydrochloric acid were removed *in vacuo*. The residue was dissolved in 110 ml of methanol and 0.9 g of 10 % of palladium on activated charcoal were added. The reaction mixture was hydrogenated (room temperature, 5 bar) for 20 h. The catalyst was filtered off and was washed three times with 50 ml portions of methanol. The filtrate was evaporated *in vacuo* and the product was purified by flash-chromatography to give 1.34 g (57%) of the title compound as a white powder.

MS m/e (%): 222 ($M+H^+$, 100).

c) 1-Cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidine hydrochloride (1:1)

To a suspension of 200 mg (0.9 mmol) 4-(2,6-dimethoxy-phenyl)-piperidine in 140 mg (0.9 mmol) cyclodecanone were added 1.28 g (4.52 mmol) tetraisopropyl orthotitanate. After stirring for 4 days at room temperature, a viscous oil was obtained. A solution of 40 mg (0.63 mmol) sodium cyanoborohydride in 1 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 5 h at room temperature and 10 ml of 2.3 N hydrochloric acid in ethanol were added. After heating for 3 h at 60°C, the solution was adjusted to pH 8 by addition of 25 % sodium hydroxide solution and filtered. The filtrate was extracted with ethyl acetate, the organic phase washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 18 mg of white crystals. The amine was dissolved in 10 ml ether and 1 ml of 2.3 M hydrochloric acid in ether was added dropwise. The solution was stirred for 30 min at room temperature and was evaporated. The residue was suspended in ether and was stirred for 1 h. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 20 mg (6%) of the title compound as a white powder.

MS m/e (%): 360 ($M+H^+$, 100).

Example 36

(3RS,4RS)-1-Cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

a) (3RS,4RS)-1-Benzyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

The title compound was prepared in comparable yield according to a literature procedure (Juan C. Jean and Lawrence D. Wise, *J. Heterocyclic Chem.* **1987**, *24*, 1317 - 1319) in three steps starting from 1,3-dimethoxyphen-2-ylmagnesium bromide instead of 2-methoxyphenylmagnesium bromide. The product was obtained as white crystals.

MS m/e (%): 328 ($M+H^+$, 100).

b) (3RS,4RS)-4-(2,6-Dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 2.9 g (8 mmol) of (3RS,4RS)-1-benzyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1) in 80 ml of methanol were added 600 mg of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature, 5 bar) until the theoretical amount of hydrogen was taken up (about 20 h). The catalyst was filtered off and was washed three times with 20 ml portions of methanol. The filtrate was evaporated *in vacuo* to give 1.88 g (87%) of the title compound as a light yellow powder.

MS m/e (%): 237 (M^+, 27), 208 (100).

c) (3RS,4RS)-4-(2,6-Dimethoxy-phenyl)-piperidin-3-ol

To a suspension of 1.78 g (6.53 mmol) (3RS,4RS)-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1) in 25 ml ethanol were added 1.0 g sodium carbonate. After stirring for 2h at room temperature, the sodium salts were filtered off and washed with 10 ml of ethanol. The filtrate was concentrated, diluted with 2-propanol and filtered again. The filtrate was evaporated to give 1.46 g (quantitative) of the title compound as a light yellow solid.

MS m/e (%): 238 ($M+H^+$, 100).

d) (3RS,4RS)-1-Cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol

To a suspension of 500 mg (2.1 mmol) (3RS,4RS)-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol in 325 mg (2.1 mmol) cyclodecanone were added 3.0 g (10.5 mmol) tetraisopropyl orthotitanate. After stirring for 4 days at room temperature, a viscous oil was obtained. A solution of 93 mg (1.5 mmol) sodium cyanoborohydride in 1.5 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 2 h at room temperature and 25 ml of 2.3 N hydrochloric acid in ethanol were added. After heating for 2 h at 60°C, the solution was adjusted to pH 8 by addition of 25 % sodium hydroxide solution and filtered. The filtrate was extracted with ethyl acetate, the organic phase washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 218 mg (27%) of the title compound as a yellow oil.

MS m/e (%): 376 ($M+H^+$, 100).

e) (3RS,4RS)-1-Cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol hydrochloride (1:1)

To a solution of 30 mg (0.08 mmol) (3RS,4RS)-1-cyclodecyl-4-(2,6-dimethoxy-phenyl)-piperidin-3-ol in 3 ml ethanol were added dropwise 0.3 ml of 2.3 M hydrochloric acid in ethanol. The solution was stirred for 30 min at room temperature and was evaporated. The residue was suspended in ether and was stirred for 1 h. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 20 mg (61%) of the title compound as a white powder.

MS m/e (%): 376 ($M+H^+$, 100).

Example 37

1-Cyclodecyl-4-phenyl-piperidine hydrochloride (1:1)

To a suspension of 200 mg (1.24 mmol) 4-phenylpiperidine in 230 mg (1.49 mmol) cyclodecanone were added 1.76 g (6.2 mmol) tetraisopropyl orthotitanate. After stirring for 5 days at room temperature, a viscous oil was obtained. A solution of 235 mg (6.2 mmol) sodium borohydride in 10 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 2 h at room temperature and 10 ml concentrated ammonia solution were added. The inorganic precipitate was filtered off and washed with dichloromethane. The filtrate was extracted with dichloromethane, the organic phase washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by

flash-chromatography to give 270 mg of a yellow solid. The amine was dissolved in 10 ml ethanol and 1 ml of 2.3 M hydrochloric acid in ethanol was added dropwise. The solution was stirred for 30 min at room temperature and was evaporated. The residue was suspended in ether and was stirred for 1 h. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 200 mg (48%) of the title compound as a white powder.

MS m/e (%): 300 ($M+H^+$, 100).

Example 38

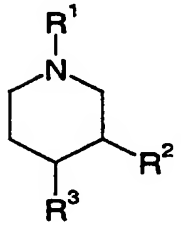
1-Cyclodecyl-4-cyclohexyl-piperidine hydrochloride (1:1)

To a suspension of 200 mg (1.12 mmol) 4-cyclohexylpiperidine in 220 mg (1.43 mmol) cyclodecanone were added 1.67 g (6.0 mmol) tetraisopropyl orthotitanate. After stirring for 5 days at room temperature, a viscous oil was obtained. A solution of 225 mg (6.0 mmol) sodium borohydride in 10 ml ethanol was added dropwise within 3-4 min. Stirring was continued for 2 h at room temperature and 10 ml concentrated ammonia solution were added. The inorganic precipitate was filtered off and washed with dichloromethane. The filtrate was extracted with dichloromethane, the organic phase washed with brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 80 mg of a light yellow solid. The amine was dissolved in 10 ml ethanol and 1 ml of 2.3 M hydrochloric acid in ethanol was added dropwise. The solution was stirred for 30 min at room temperature and was evaporated. The residue was suspended in ether and was stirred for 1 h. The precipitate was filtered off, washed with ether and dried *in vacuo* to give 78 mg (19%) of the title compound as a white powder.

MS m/e (%): 305 (M^+, 18), 206 (100).

Claims

1. Compounds of the general formula



I

wherein

R^1 is tetrahydronaphtyl;

or $-(CH_2)_n-C_6H_5-R^4$ wherein n is 0-4 and R^4 is H, lower alkyl, or lower alkoxy;

or C_5-C_{12} cycloalkyl, optionally substituted by lower alkyl;

R^2 is H, OH, lower alkoxy, lower alkenyloxy or lower alkyl;

R^3 is C_5-C_7 cycloalkyl or phenyl, optionally substituted by OH, halogen, lower alkoxy, lower alkenyloxy, lower alkyl or $-O-(CH_2)_n-C_6H_5$ wherein n is 0-3;

and their pharmaceutically acceptable acid addition salts.

2. Compounds according to claim 1 wherein R^1 is C_5-C_{12} cycloalkyl, optionally substituted by lower alkyl.

3. Compounds according to claim 2, being

(3RS,4RS)-1-cyclononyl-4-(2-hydroxy-phenyl)piperidin-3-ol;

1-cyclodecyl-4-(2-methoxy-phenyl)-piperidine;

(3RS,4RS)-1-cyclodecyl-4-(2-isopropyl-phenyl)piperidin-3-ol;

(3RS,4RS)-4-(2-hydroxy-phenyl)-1-(cis-and-(trans-4-isopropylcyclohexyl)-piperidin-3-ol;

2-(1-cyclodecyl-piperidin-4-yl)-phenol;

(3RS,4RS)-1-cyclodecyl-4-(2-methoxy-phenyl)-piperidin-3-ol;

1-cyclodecyl-4-cyclohexyl-piperidine;

(3RS,4RS)-1-cyclononyl-4-(2-methoxy-phenyl)-piperidin-3-ol;

(3RS,4RS)-4-(2-allyloxy-phenyl)-1-cyclodecyl-piperidin-3-ol;

1-cyclodecyl-4-phenyl-piperidine;

(3RS,4RS)-1-cyclononyl-4-(2-isopropyl-phenyl)-piperidin-3-ol; and

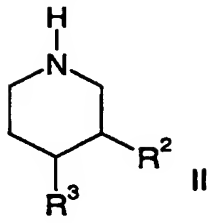
(3RS,4RS)-1-cyclodecyl-4-(2-hydroxy-phenyl)piperidin-3-ol.

4. Compounds according to anyone of claims 1-3 for use as therapeutic active substances, in particular for memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias such as vascular dementia and AIDS dementia complex, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain conditions, withdrawal symptoms of addictive drugs and reduction of their abuse/craving, control of water balance, Na^+ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

5. A medicament containing one or more compounds of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof .

6..A medicament according to claim 5 for the treatment of Orphanin FQ (OFQ) receptor related diseases, which include memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias such as vascular dementia and AIDS dementia complex, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain conditions, withdrawal symptoms of addictive drugs and reduction of their abuse/craving, control of water balance, Na^+ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

7. A process for preparing a compound of formula I as defined in claim 1, which process comprises reductively aminating a compound of formula II



II

with a compound of formula

IV

wherein R^1, R^2 and R^3 are as claimed in claim 1.

8. The use of one or more compounds according to claims 1 to 3, or pharmaceutically acceptable salts thereof, for the manufacture of medicaments.

9. The use according to claim 8 for the manufacture of a medicament for the treatment of memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias such as vascular dementia and AIDS dementia complex, Parkinson's disease, epilepsy and convulsions, acute and/or chronic pain conditions, withdrawal symptoms of addictive drugs and reduction of their abuse/craving, control of water balance, Na^+ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

10. Compounds of the general formula I, obtained by the process of claim 7 or by equivalent processes.

11. The invention substantially as described herein.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06442

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/42 C07D211/22 C07D211/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 00313 A (UNIV VIRGINIA COMMONWEALTH) 7 January 1993 (1993-01-07) examples 39,81,82,165	1,4-6,8, 9
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 November 1999	30/11/1999

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